1. NAME OF THE MEDICINAL PRODUCT

NEOSTIGMINE METHYL SULFATE INJECTION BP 2.5 MG/ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:

Each ml contains:

Neostigmine Methyl Sulfate BP 2.5 mg

3. PHARMACEUTICAL FORM

A clear colorless solution for Injection**.**

4. Clinical particulars

4.1 Therapeutic indications

Myasthenia Gravis, antagonist to non-depolarizing neuromuscular blockade, Paralytic Ileus, Post-operative Urinary Retention; Paroxysmal Supraventricular Tachycardia.

4.2 Posology and method of administration

Posology:

Recommended doses are present by indication below but may be varied according to the individual needs of the patient.

Myasthenia Gravis

Patient population	**Recommended dose (via subcutaneous or intramuscular injection)**
Adults and Children (12 to 17 years)	1 – 2.5 mg Neostigmine Methylsulfate repeated at suitable intervals throughout the day (usual total daily dose in adults is 5 – 20 mg).
Children (1 month to 11 years)	200 to 500 micrograms Neostigmine Methylsulfate repeated at suitable intervals throughout the day
Neonates (up to 1 month)	150 micrograms/kg Neostigmine Methylsulfate every 6 – 8 hours, to be given 30 minutes before feeds, then increased if necessary up to 300 micrograms/kg every 4 hours. Because of the self-limiting nature of the disease in neonates, the daily dosage should be reduced until the drug can be withdrawn.

Antagonist to Non-depolarizing Neuromuscular Blockade

Reversal of Neuromuscular blockade with Neostigmine should not be attempted unless there is spontaneous recovery from paralysis.

Atropine and Neostigmine may be given simultaneously, but in patients with Bradycardia, the pulse rate should be increased to 80 per minute with Atropine before administering Neostigmine.

Patient population	**Recommended dose (via intravenous injection)**
Adults	2.5 mg Neostigmine Methylsulfate (maximum per dose 5 mg), to be given over 1 minute, after or with glycopyrronium or atropine. Repeat if necessary.
Children (12 to 17 years)	50 micrograms Neostigmine Methylsulfate per kg bodyweight (maximum per dose 2.5 mg Neostigmine Methylsulfate) to be given over 1 minute after or with glycopyrronium or atropine, followed by a further dose of 25 micrograms/kg Neostigmine Methylsulfate if required.
Children (1 month to 11 years)	50 micrograms Neostigmine Methylsulfate per kg bodyweight (maximum per dose 2.5 mg Neostigmine Methylsulfate) to be given over 1 minute after or with glycopyrronium or atropine, followed by a further dose of 25 micrograms/kg Neostigmine Methylsulfate if required.
Neonates (up to 1 month)	50 micrograms Neostigmine Methylsulfate per kg bodyweight to be given over 1 minute after or with glycopyrronium or atropine, followed by a further dose of 25 micrograms/kg Neostigmine Methylsulfate if required.

Other Indications

Paralytic ileus and post-operative urinary retention

Patient population	Recommended dose (via subcutaneous or intramuscular injection)
Adults	0.5 – 2.5 mg Neostigmine Methylsulfate.
Children	0.125 – 1 mg Neostigmine Methylsulfate.

Paroxysmal supraventricular tachycardia (via IV injection)

Treatment should be reserved for severe cases not responding to conventional treatment and under the close supervision of a specialist experienced with its use.

Use in special population groups

Paediatric population

A posology for use in the paediatric population is presented above by indication.

Use in the elderly

There are no specific dosage recommendations for Neostigmine Methylsulfate in the elderly.

Method of administration:

Neostigmine Methylsulfate may be administered by IV, IM or SC injection. Please refer to the above text for the recommended route of administration according to indication.

Neostigmine Methylsulfate should be given slowly by the IV route (given over 1 minute).

A syringe of Atropine Sulfate should always be available to counteract severe cholinergic reactions should they occur.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Neostigmine should not be administered to patients with mechanical obstruction of gastrointestinal or urinary tracts, peritonitis or doubtful bowel viability.

Neostigmine should not be used in conjunction with depolarising muscle relaxants such as suxamethonium as neuromuscular blockade may be potentiated.

4.4 Special warnings and precautions for use

Neostigmine should be used with extreme caution in patients with asthma as the parasympathomimetic action of neostigmine may cause bronchoconstriction.

Bradycardia, with the potential for progression to asystole, may occur in patients receiving neostigmine by intravenous injection unless atropine is given simultaneously. Extreme caution should be employed when treating patients with pre-existing bradycardia, cardiac arrhythmia or recent coronary occlusion.

Patients who are hyperreactive to neostigmine experience a severe cholinergic reaction to the drug. Atropine sulfate should always be available as an antagonist for the muscarinic effects of neostigmine.

Neostigmine should be used with caution in patients with epilepsy, vagotonia, hyperthyroidism, peptic ulceration or parkinsonism.

Administration of anticholinesterase agents to patients with intestinal anastomoses may produce rupture of the anastomosis or leakage of intestinal contents.

Elderly

Although there are no specific dosage requirements in the elderly, these patients may be more susceptible to dysrhythmias than younger patients.

Inhaled anaesthetics

Neostigmine Methylsulfate should not be given during cyclopropane or halothane anaesthesia; although it may be used after withdrawal of these agents.

Sodium content

This medicine contains 3.54 mg (or 0.15 mmol) sodium per each 1 ml ampoule (i.e. less than 1 mmol sodium (23 mg) per 1 ml ampoule), that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Neuromuscular Blocking Agents

Neostigmine effectively antagonises the effect of Non-depolarizing muscle relaxants (e.g. Tubocurarine, Gallamine or Pancuronium) and this interaction is used to therapeutic advantage to reverse muscle relaxation after surgery. Neostigmine does not antagonise, and it may in fact prolong, the phase I block of depolarizing muscle relaxants such as Succinylcholine.

Other Drugs

Atropine antagonises the muscarinic effects of Neostigmine, the interaction is utilised to counteract the muscarinic symptoms of the Neostigmine toxicity.

Anticholinesterase agents are sometimes effective in reversing Neuromuscular Block induced by Aminoglycoside Antibiotics. However, Aminoglycoside Antibiotics and other drugs that interfere with Neuromuscular transmission should be used cautiously, if at all, in patients with Myasthenia Gravis and the dose of Neostigmine may have to be adjusted accordingly.

4.6 Pregnancy and Lactation

The use of Neostigmine Methylsulfate during pregnancy or lactation has not been established. Although the possible hazards to mother and child must be weighed against the potential benefits in every case. Experience with Myasthenia Gravis has revealed no untoward effect of the drug on the course of pregnancy. As the severity of Myasthenia Gravis often fluctuates considerably, particular care is required to avoid cholinergic crisis due to overdosage of Neostigmine.

Only negligible amounts of Neostigmine Methylsulfate are excreted in breast milk. Nevertheless, attention should be paid to possible effects on the breast-feeding infant.

4.7 Effects on ability to drive and use machines

Not applicable..

4.8 Undesirable effects

Adverse effects of Neostigmine are chiefly those of exaggerated response to parasympathetic stimulation.

System Organ Class	Adverse reaction	Frequency
Immune system disorders	Hypersensitivity, angioedema, anaphylactic reaction.	Not known
Nervous system disorders	Cholinergic syndrome, especially at high doses. In patients with myasthenia gravis, cholinergic crisis may be difficult to distinguish from myasthenia crisis (see section 4.9).	Not known
Eye disorders	Miosis, lacrimation increased	Not known
Cardiac disorders	Bradycardia, decreased cardiac conduction, in severe cases possibly leading to heart block or cardiac arrest	Not known
Vascular disorders	Hypotension	Not known
Respiratory, thoracic or mediastinal disorders	Increased bronchial secretion, bronchospasm	Not known
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal	Not known

	cramps, salivary hypersecretion. Increased intestinal motility may result in involuntary defecation.	
Skin and subcutaneous tissue disorders	Hyperhidrosis	Not known
Musculoskeletal, connective tissue and bone disorders	Muscle spasms	Not known
Renal and urinary disorders	Urinary incontinence	Not known

4.9 Overdose

Symptoms

Neostigmine Methylsulfate overdosage may include Cholinergic Crisis, which is characterised by nausea, vomiting, diarrhoea, excessive salivation and sweating, increased bronchial secretions, miosis, bradycardia or tachycardia, cardiospasm, bronchospasm, incoordination, muscle cramps, fasciculation and paralysis. Extremely high doses may produce CNS symptoms of agitation, fear or restlessness. Death may result from cardiac arrest or respiratory paralysis and pulmonary oedema. In patients with Myasthenia Gravis, in whom overdosage is most likely to occur, fasciculation and adverse parasympathomimetic effects may be mild or absent making cholinergic crisis difficult to distinguish from Myasthenia crisis.

Treatment

Maintenance of adequate respiration is of primary importance. Tracheostomy, Bronchial aspiration and postural drainage may be required; Respiration can be assisted mechanically or with oxygen, if necessary.

Neostigmine Methylsulfate should be discontinued immediately and 1 – 4mg of Atropine Sulfate administered IV. Additional doses of Atropine may be given every 5 – 30 minutes as needed to control muscarinic symptoms. Atropine overdosage should be avoided as tenacious secretions and bronchial plugs may result.

5. PHARMACOLOGICAL PROPERTIES

Pharmacodynamics properties

Neostigmine inhibits cholinesterase activity and prolongs and intensifies the muscarinic and nicotinic effects of acetylcholine. The anticholinesterase actions of Neostigmine are reversible. It is used mainly for its action on skeletal muscle and less frequently to increase the activity of smooth muscle. Neostigmine is used in the treatment of Myasthenia Gravis.

5.1 Pharmacokinetic properties

Neostigmine is a quaternary ammonium compound and is poorly absorbed from the gastrointestinal tract. Following parenteral administration as the methylsulfate, neostigmine is metabolised partly by hydrolysis of the ester linkage and is excreted in the urine both as unchanged drug and as metabolites. The half-life of neostigmine is only one to two hours.

5.2 Preclinical safety data

No further information other than that which is included in the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Neostigmine Methyl Sulphate

Sodium Chloride

Disodium EDTA

Sodium Hydroxide

Sodium Acetate

Water for Injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Month

6.4 Special precautions for storage

Protect from light.

6.5 Nature and contents of container <and special equipment for use, administration or implantation

1 ml Amber USP Type I Ampoule

6.6 Special precautions for disposal <and other handling>

No special requirements

7. APPLICANT/MANUFACTURER

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